```
(FILE 'HOME' ENTERED AT 14:57:21 ON 06 JUL 2011)

     FILE 'REGISTRY' ENTERED AT 14:58:30 ON 06 JUL 2011
                  E GLUFOSFAMIDE/CN
L1              1 S GLUFOSFAMIDE/CN
                  SEL CHEM
                  E GEMCITABINE/CN
L2              5 S E19-23
                  SEL CHEM

     FILE 'HCAPLUS' ENTERED AT 15:00:38 ON 06 JUL 2011
L3             73 S E13-E16
L4           8002 S E29-E59
L5             10 S L3 (L) L4
L6             24 S L3 AND L4

     FILE 'STNGUIDE' ENTERED AT 15:01:53 ON 06 JUL 2011

     FILE 'HCAPLUS' ENTERED AT 15:07:09 ON 06 JUL 2011
L7             14 S L6 NOT L5

     FILE 'STNGUIDE' ENTERED AT 15:07:34 ON 06 JUL 2011

=> s L3 (L) (pancreatic OR pancreas)
            18 "D"/BI
             0 "19575"/BI
             0 "D 19575"/BI
                 (("D"(W)"19575")/BI)
             0 "GLUCOSYLIFOSFAMIDE"/BI
             0 "MUSTARD"/BI
             0 "GLUCOSYLIFOSFAMIDE MUSTARD"/BI
                 (("GLUCOSYLIFOSFAMIDE"(W)"MUSTARD")/BI)
             0 GLUFOSFAMIDE/BI
             0 132682/BI
             0 98/BI
            92 5/BI
             0 132682-98-5/BI
                 ((132682(W)98(W)5)/BI)
             0 PANCREATIC
L8           0 L3 (L) (PANCREATIC OR PANCREAS)

=> s L3 AND (pancreatic OR pancreas OR metastasis OR metastatic OR tumor)
            18 "D"/BI
             0 "19575"/BI
             0 "D 19575"/BI
                 (("D"(W)"19575")/BI)
             0 "GLUCOSYLIFOSFAMIDE"/BI
             0 "MUSTARD"/BI
             0 "GLUCOSYLIFOSFAMIDE MUSTARD"/BI
                 (("GLUCOSYLIFOSFAMIDE"(W)"MUSTARD")/BI)
             0 GLUFOSFAMIDE/BI
             0 132682/BI
             0 98/BI
            92 5/BI
             0 132682-98-5/BI
                 ((132682(W)98(W)5)/BI)
             0 PANCREATIC
             0 PANCREAS
             0 METASTASIS
             0 METASTATIC
L9           0 L3 AND (PANCREATIC OR PANCREAS OR METASTASIS OR METASTATIC OR
```

```
                TUMOR)

=> s L4 AND (pancreatic OR pancreas OR metastasis OR metastatic OR tumor)
             0 DDFC/BI
             0 DFDC/BI
             0 DFDCTP/BI
             0 DFDCYD/BI
             0 FOLFUGEM/BI
             0 GAMCITABINE/BI
             0 GEMCEL/BI
             0 "GEMCITABINE"/BI
             0 "HYDROCHLORIDE"/BI
             0 "GEMCITABINE HYDROCHLORIDE"/BI
                 (("GEMCITABINE"(W)"HYDROCHLORIDE")/BI)
             0 "GEMCITABINE"/BI
             0 "MONOPHOSPHATE"/BI
             0 "GEMCITABINE MONOPHOSPHATE"/BI
                 (("GEMCITABINE"(W)"MONOPHOSPHATE")/BI)
             0 "GEMCITABINE"/BI
             0 "TRIPHOSPHATE"/BI
             0 "GEMCITABINE TRIPHOSPHATE"/BI
                 (("GEMCITABINE"(W)"TRIPHOSPHATE")/BI)
             0 "GEMCITABINE"/BI
            92 "5"/BI
             0 "DIPHOSPHATE"/BI
             0 "GEMCITABINE 5'-DIPHOSPHATE"/BI
                 (("GEMCITABINE"(W)"5"(W)"DIPHOSPHATE")/BI)
             0 GEMCITABINE/BI
             0 GEMCITERA/BI
             0 GEMLIP/BI
             0 GEMSAR/BI
             0 GEMZAR/BI
             0 "LY"/BI
             0 "188011"/BI
             0 "HYDROCHLORIDE"/BI
             0 "LY 188011 HYDROCHLORIDE"/BI
                 (("LY"(W)"188011"(W)"HYDROCHLORIDE")/BI)
             0 "LY"/BI
             0 "188011"/BI
             0 "LY 188011"/BI
                 (("LY"(W)"188011")/BI)
             1 "NSC"/BI
             0 "613327"/BI
             0 "NSC 613327"/BI
                 (("NSC"(W)"613327")/BI)
             0 ZEFEI/BI
             0 110988/BI
             0 86/BI
            52 8/BI
             0 110988-86-8/BI
                 ((110988(W)86(W)8)/BI)
             0 116371/BI
             0 66/BI
            92 5/BI
             0 116371-66-5/BI
                 ((116371(W)66(W)5)/BI)
             0 116371/BI
             0 67/BI
            73 6/BI
             0 116371-67-6/BI
                 ((116371(W)67(W)6)/BI)
```

```
              0 122111/BI
             28 03/BI
             40 9/BI
              0 122111-03-9/BI
                  ((122111(W)03(W)9)/BI)
              0 1239668/BI
              0 67/BI
             55 7/BI
              0 1239668-67-7/BI
                  ((1239668(W)67(W)7)/BI)
            170 "2"/BI
              0 "DEOXY"/BI
            170 "2"/BI
            170 "2"/BI
              0 "DIFLUOROCYTIDINE"/BI
              0 "2'-DEOXY-2',2'-DIFLUOROCYTIDINE"/BI
                  (("2"(W)"DEOXY"(W)"2"(W)"2"(W)"DIFLUOROCYTIDINE")/BI)
            170 "2"/BI
            170 "2"/BI
              0 "DIFLUORO"/BI
            170 "2"/BI
              0 "DEOXYCYTIDINE"/BI
              0 "TRIPHOSPHATE"/BI
              0 "2',2'-DIFLUORO-2'-DEOXYCYTIDINE TRIPHOSPHATE"/BI
                  (("2"(W)"2"(W)"DIFLUORO"(W)"2"(W)"DEOXYCYTIDINE"(W)"TRIPHOSPHA
                 TE")/BI)
            170 "2"/BI
            170 "2"/BI
              0 "DIFLUORO"/BI
            170 "2"/BI
              0 "DEOXYCYTIDINE"/BI
              0 "2',2'-DIFLUORO-2'-DEOXYCYTIDINE"/BI
                  (("2"(W)"2"(W)"DIFLUORO"(W)"2"(W)"DEOXYCYTIDINE")/BI)
            170 "2"/BI
            170 "2"/BI
              0 "DIFLUORODEOXYCYTIDINE"/BI
             92 "5"/BI
              0 "TRIPHOSPHATE"/BI
              0 "2',2'-DIFLUORODEOXYCYTIDINE 5'-TRIPHOSPHATE"/BI
                  (("2"(W)"2"(W)"DIFLUORODEOXYCYTIDINE"(W)"5"(W)"TRIPHOSPHATE")/
                 BI)
            170 "2"/BI
            170 "2"/BI
              0 "DIFLUORODEOXYCYTIDINE"/BI
              0 "2',2'-DIFLUORODEOXYCYTIDINE"/BI
                  (("2"(W)"2"(W)"DIFLUORODEOXYCYTIDINE")/BI)
              0 95058/BI
              1 81/BI
            125 4/BI
              0 95058-81-4/BI
                  ((95058(W)81(W)4)/BI)
L10           0 L4 AND (PANCREATIC OR PANCREAS OR METASTASIS OR METASTATIC OR
                TUMOR)

=> file hcaplus
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 1.04     139.33

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                   ENTRY    SESSION
```

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FILE 'HCAPLUS' ENTERED AT 15:15:32 ON 06 JUL 2011
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 6 Jul 2011 VOL 155 ISS 2
FILE LAST UPDATED: 5 Jul 2011 (20110705/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Apr 2011
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Apr 2011

HCAplus now includes complete International Patent Classification (IPC)
reclassification data for the first quarter of 2011.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate
substance identification.

```
=> s L4 AND (pancreatic OR pancreas OR metastasis OR metastatic OR tumor)
        109536 PANCREATIC
             6 PANCREATICS
        109537 PANCREATIC
                  (PANCREATIC OR PANCREATICS)
        103629 PANCREAS
           944 PANCREASES
        103802 PANCREAS
                  (PANCREAS OR PANCREASES)
         95012 METASTASIS
            17 METASTASISES
         23212 METASTASES
        102840 METASTASIS
                  (METASTASIS OR METASTASISES OR METASTASES)
         46953 METASTATIC
             1 METASTATICS
         46954 METASTATIC
                  (METASTATIC OR METASTATICS)
        603091 TUMOR
        211336 TUMORS
        666735 TUMOR
                  (TUMOR OR TUMORS)
          5543 TUMOUR
          2023 TUMOURS
          7430 TUMOUR
                  (TUMOUR OR TUMOURS)
        667239 TUMOR
                  (TUMOR OR TUMOUR)
```

```
L11       5280 L4 AND (PANCREATIC OR PANCREAS OR METASTASIS OR METASTATIC OR
               TUMOR)

=> s L3 AND (pancreatic OR pancreas OR metastasis OR metastatic OR tumor)
        109536 PANCREATIC
             6 PANCREATICS
        109537 PANCREATIC
                 (PANCREATIC OR PANCREATICS)
        103629 PANCREAS
           944 PANCREASES
        103802 PANCREAS
                 (PANCREAS OR PANCREASES)
         95012 METASTASIS
            17 METASTASISES
         23212 METASTASES
        102840 METASTASIS
                 (METASTASIS OR METASTASISES OR METASTASES)
         46953 METASTATIC
             1 METASTATICS
         46954 METASTATIC
                 (METASTATIC OR METASTATICS)
        603091 TUMOR
        211336 TUMORS
        666735 TUMOR
                 (TUMOR OR TUMORS)
          5543 TUMOUR
          2023 TUMOURS
          7430 TUMOUR
                 (TUMOUR OR TUMOURS)
        667239 TUMOR
                 (TUMOR OR TUMOUR)
L12         40 L3 AND (PANCREATIC OR PANCREAS OR METASTASIS OR METASTATIC OR
               TUMOR)

=> s L4 (L) (pancreatic OR pancreas OR metastasis OR metastatic OR tumor)
        109536 PANCREATIC
             6 PANCREATICS
        109537 PANCREATIC
                 (PANCREATIC OR PANCREATICS)
        103629 PANCREAS
           944 PANCREASES
        103802 PANCREAS
                 (PANCREAS OR PANCREASES)
         95012 METASTASIS
            17 METASTASISES
         23212 METASTASES
        102840 METASTASIS
                 (METASTASIS OR METASTASISES OR METASTASES)
         46953 METASTATIC
             1 METASTATICS
         46954 METASTATIC
                 (METASTATIC OR METASTATICS)
        603091 TUMOR
        211336 TUMORS
        666735 TUMOR
                 (TUMOR OR TUMORS)
          5543 TUMOUR
          2023 TUMOURS
          7430 TUMOUR
                 (TUMOUR OR TUMOURS)
        667239 TUMOR
```

```
                (TUMOR OR TUMOUR)
L13        3854 L4 (L) (PANCREATIC OR PANCREAS OR METASTASIS OR METASTATIC OR
                TUMOR)

=> s L3 (L) (pancreatic OR pancreas OR metastasis OR metastatic OR tumor)
        109536 PANCREATIC
             6 PANCREATICS
        109537 PANCREATIC
                (PANCREATIC OR PANCREATICS)
        103629 PANCREAS
           944 PANCREASES
        103802 PANCREAS
                (PANCREAS OR PANCREASES)
         95012 METASTASIS
            17 METASTASISES
         23212 METASTASES
        102840 METASTASIS
                (METASTASIS OR METASTASISES OR METASTASES)
         46953 METASTATIC
             1 METASTATICS
         46954 METASTATIC
                (METASTATIC OR METASTATICS)
        603091 TUMOR
        211336 TUMORS
        666735 TUMOR
                (TUMOR OR TUMORS)
          5543 TUMOUR
          2023 TUMOURS
          7430 TUMOUR
                (TUMOUR OR TUMOURS)
        667239 TUMOR
                (TUMOR OR TUMOUR)
L14         29 L3 (L) (PANCREATIC OR PANCREAS OR METASTASIS OR METASTATIC OR
                TUMOR)

=> s l14 AND (ad<=20050204 OR pd<=20050204 OR prd<20050204)
       5223994 AD<=20050204
                (AD<=20050204)
      25992394 PD<=20050204
                (PD<=20050204)
       4694294 PRD<20050204
                (PRD<20050204)
L15         16 L14 AND (AD<=20050204 OR PD<=20050204 OR PRD<20050204)

=> s l13 AND (ad<=20050204 OR pd<=20050204 OR prd<20050204)
       5223994 AD<=20050204
                (AD<=20050204)
      25992394 PD<=20050204
                (PD<=20050204)
       4694294 PRD<20050204
                (PRD<20050204)
L16       1546 L13 AND (AD<=20050204 OR PD<=20050204 OR PRD<20050204)

=> s l15 NOT l7
L17         15 L15 NOT L7

=> d l17 ibib abs hit

L17  ANSWER 1 OF 15  HCAPLUS  COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER:         2006:6713  HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER:          145:33
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TITLE: Metabolism and Transport of Oxazaphosphorines and the Clinical Implications

AUTHOR(S): Zhang, Jing; Tian, Quan; Chan, Sui Yung; Li, Shu Chuen; Zhou, Shufeng; Duan, Wei; Zhu, Yi-Zhun

CORPORATE SOURCE: Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore, Singapore

SOURCE: Drug Metabolism Reviews (2005), 37(4), 611-703
CODEN: DMTRAR; ISSN: 0360-2532

PUBLISHER: Taylor & Francis, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The oxazaphosphorines including cyclophosphamide (CPA), ifosfamide (IFO), and trofosfamide represent an important group of therapeutic agents due to their substantial antitumor and immuno-modulating activity. CPA is widely used as an anticancer drug, an immunosuppressant, and for the mobilization of hematopoietic progenitor cells from the bone marrow into peripheral blood prior to bone marrow transplantation for aplastic anemia, leukemia, and other malignancies. New oxazaphosphorines derivs. have been developed in an attempt to improve selectivity and response with reduced toxicity. These derivs. include mafosfamide (NSC 345842), glufosfamide (D19575, β-D-glucosylisophosphoramide mustard), NSC 612567 (aldophosphamide perhydrothiazine), and NSC 613060 (aldophosphamide thiazolidine). This review highlights the metabolism and transport of these oxazaphosphorines (mainly CPA and IFO, as these two oxazaphosphorine drugs are the most widely used alkylating agents) and the clin. implications. Both CPA and IFO are prodrugs that require activation by hepatic cytochrome P 450 (CYP)-catalyzed 4-hydroxylation, yielding cytotoxic nitrogen mustards capable of reacting with DNA mols. to form crosslinks and lead to cell apoptosis and/or necrosis. Such prodrug activation can be enhanced within tumor cells by the CYP-based gene directed-enzyme prodrug therapy (GDEPT) approach. However, those newly synthesized oxazaphosphorine derivs. such as glufosfamide, NSC 612567 and NSC 613060, do not need hepatic activation. They are activated through other enzymic and/or non-enzymic pathways. For example, both NSC 612567 and NSC 613060 can be activated by plain phosphodiesterase (PDEs) in plasma and other tissues or by the high-affinity nuclear 3'-5' exonucleases associated with DNA polymerases, such as DNA polymerases and ε. The alternative CYP-catalyzed inactivation pathway by N-dechloroethylation generates the neurotoxic and nephrotoxic byproduct chloroacetaldehyde (CAA). Various aldehyde dehydrogenases (ALDHs) and glutathione S-transferases (GSTs) are involved in the detoxification of oxazaphosphorine metabolites. The metabolism of oxazaphosphorines is auto-inducible, with the activation of the orphan nuclear receptor pregnane X receptor (PXR) being the major mechanism. Oxazaphosphorine metabolism is affected by a number of factors associated with the drugs (e.g., dosage, route of administration, chirality, and drug combination) and patients (e.g., age, gender, renal and hepatic function). Several drug transporters, such as breast cancer resistance protein (BCRP), multidrug resistance associated proteins (MRP1, MRP2, and MRP4) are involved in the active uptake and efflux of parental oxazaphosphorines, their cytotoxic mustards and conjugates in hepatocytes and tumor cells. Oxazaphosphorine metabolism and transport have a major impact on pharmacokinetic variability, pharmacokinetic-pharmacodynamic relationship, toxicity, resistance, and drug interactions since the drug-metabolizing enzymes and drug transporters involved are key determinants of the pharmacokinetics and pharmacodynamics of oxazaphosphorines. A better understanding of the factors that affect the metabolism and transport of oxazaphosphorines is important for their optional use in cancer chemotherapy.

REFERENCE COUNT: 636 THERE ARE 636 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Drug Metabolism Reviews (2005), 37(4), 611-703
CODEN: DMTRAR; ISSN: 0360-2532

AB A review. The oxazaphosphorines including cyclophosphamide (CPA), ifosfamide (IFO), and trofosfamide represent an important group of therapeutic agents due to their substantial antitumor and immuno-modulating activity. CPA is widely used as an anticancer drug, an immunosuppressant, and for the mobilization of hematopoietic progenitor cells from the bone marrow into peripheral blood prior to bone marrow transplantation for aplastic anemia, leukemia, and other malignancies. New oxazaphosphorines derivs. have been developed in an attempt to improve selectivity and response with reduced toxicity. These derivs. include mafosfamide (NSC 345842), glufosfamide (D19575, β-D-glucosylisophosphoramide mustard), NSC 612567 (aldophosphamide perhydrothiazine), and NSC 613060 (aldophosphamide thiazolidine). This review highlights the metabolism and transport of these oxazaphosphorines (mainly CPA and IFO, as these two oxazaphosphorine drugs are the most widely used alkylating agents) and the clin. implications. Both CPA and IFO are prodrugs that require activation by hepatic cytochrome P 450 (CYP)-catalyzed 4-hydroxylation, yielding cytotoxic nitrogen mustards capable of reacting with DNA mols. to form crosslinks and lead to cell apoptosis and/or necrosis. Such prodrug activation can be enhanced within tumor cells by the CYP-based gene directed-enzyme prodrug therapy (GDEPT) approach. However, those newly synthesized oxazaphosphorine derivs. such as glufosfamide, NSC 612567 and NSC 613060, do not need hepatic activation. They are activated through other enzymic and/or non-enzymic pathways. For example, both NSC 612567 and NSC 613060 can be activated by plain phosphodiesterase (PDEs) in plasma and other tissues or by the high-affinity nuclear 3'-5' exonucleases associated with DNA polymerases, such as DNA polymerases and ε. The alternative CYP-catalyzed inactivation pathway by N-dechloroethylation generates the neurotoxic and nephrotoxic byproduct chloroacetaldehyde (CAA). Various aldehyde dehydrogenases (ALDHs) and glutathione S-transferases (GSTs) are involved in the detoxification of oxazaphosphorine metabolites. The metabolism of oxazaphosphorines is auto-inducible, with the activation of the orphan nuclear receptor pregnane X receptor (PXR) being the major mechanism. Oxazaphosphorine metabolism is affected by a number of factors associated with the drugs (e.g., dosage, route of administration, chirality, and drug combination) and patients (e.g., age, gender, renal and hepatic function). Several drug transporters, such as breast cancer resistance protein (BCRP), multidrug resistance associated proteins (MRP1, MRP2, and MRP4) are involved in the active uptake and efflux of parental oxazaphosphorines, their cytotoxic mustards and conjugates in hepatocytes and tumor cells. Oxazaphosphorine metabolism and transport have a major impact on pharmacokinetic variability, pharmacokinetic-pharmacodynamic relationship, toxicity, resistance, and drug interactions since the drug-metabolizing enzymes and drug transporters involved are key determinants of the pharmacokinetics and pharmacodynamics of oxazaphosphorines. A better understanding of the factors that affect the metabolism and transport of oxazaphosphorines is important for their optional use in cancer chemotherapy.

=> d l17 2-15 ibib abs hit

L17 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2005:1275117 HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER: 144:403567
TITLE: Insights into oxazaphosphorine resistance and possible

approaches to its circumvention

AUTHOR(S): Zhang, Jing; Tian, Quan; Chan, Sui Yung; Duan, Wei; Zhou, Shufeng

CORPORATE SOURCE: Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore, 117543, Singapore

SOURCE: Drug Resistance Updates (2005), 8(5), 271-297
CODEN: DRUPFW; ISSN: 1368-7646

PUBLISHER: Elsevier Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The oxazaphosphorines cyclophosphamide, ifosfamide and trofosfamide remain a clin. useful class of anticancer drugs with substantial antitumor activity against a variety of solid tumors and hematol. malignancies. A major limitation to their use is tumor resistance, which is due to multiple mechanisms that include increased DNA repair, increased cellular thiol levels, glutathione S-transferase and aldehyde dehydrogenase activities, and altered cell-death response to DNA damage. These mechanisms have been recently re-examined with the aid of sensitive anal. techniques, high-throughput proteomic and genomic approaches, and powerful pharmacogenetic tools. Oxazaphosphorine resistance, together with dose-limiting toxicity (mainly neutropenia and neurotoxicity), significantly hinders chemotherapy in patients, and hence, there is compelling need to find ways to overcome it. Four major approaches are currently being explored in preclin. models, some also in patients: combination with agents that modulate cellular response and disposition of oxazaphosphorines; antisense oligonucleotides directed against specific target genes; introduction of an activating gene (CYP3A4) into tumor tissue; and modification of dosing regimens. Of these approaches, antisense oligonucleotides and gene therapy are perhaps more speculative, requiring detailed safety and efficacy studies in preclin. models and in patients. A fifth approach is the design of novel oxazaphosphorines that have favorable pharmacokinetic and pharmacodynamic properties and are less vulnerable to resistance. Oxazaphosphorines not requiring hepatic CYP-mediated activation (for example, NSC 613060 and mafosfamide) or having addnl. targets (for example, glufosfamide that also targets glucose transport) have been synthesized and are being evaluated for safety and efficacy. Characterization of the mol. targets associated with oxazaphosphorine resistance may lead to a deeper understanding of the factors critical to the optimal use of these agents in chemotherapy and may allow the development of strategies to overcome resistance.

OS.CITING REF COUNT: 21 THERE ARE 21 CAPLUS RECORDS THAT CITE THIS RECORD (21 CITINGS)

REFERENCE COUNT: 124 THERE ARE 124 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Drug Resistance Updates (2005), 8(5), 271-297
CODEN: DRUPFW; ISSN: 1368-7646

AB A review. The oxazaphosphorines cyclophosphamide, ifosfamide and trofosfamide remain a clin. useful class of anticancer drugs with substantial antitumor activity against a variety of solid tumors and hematol. malignancies. A major limitation to their use is tumor resistance, which is due to multiple mechanisms that include increased DNA repair, increased cellular thiol levels, glutathione S-transferase and aldehyde dehydrogenase activities, and altered cell-death response to DNA damage. These mechanisms have been recently re-examined with the aid of sensitive anal. techniques, high-throughput proteomic and genomic approaches, and powerful pharmacogenetic tools. Oxazaphosphorine resistance, together with dose-limiting toxicity (mainly neutropenia and neurotoxicity), significantly hinders chemotherapy in patients, and hence, there is compelling need to find ways to overcome it. Four major

approaches are currently being explored in preclin. models, some also in patients: combination with agents that modulate cellular response and disposition of oxazaphosphorines; antisense oligonucleotides directed against specific target genes; introduction of an activating gene (CYP3A4) into tumor tissue; and modification of dosing regimens. Of these approaches, antisense oligonucleotides and gene therapy are perhaps more speculative, requiring detailed safety and efficacy studies in preclin. models and in patients. A fifth approach is the design of novel oxazaphosphorines that have favorable pharmacokinetic and pharmacodynamic properties and are less vulnerable to resistance. Oxazaphosphorines not requiring hepatic CYP-mediated activation (for example, NSC 613060 and mafosfamide) or having addnl. targets (for example, glufosfamide that also targets glucose transport) have been synthesized and are being evaluated for safety and efficacy. Characterization of the mol. targets associated with oxazaphosphorine resistance may lead to a deeper understanding of the factors critical to the optimal use of these agents in chemotherapy and may allow the development of strategies to overcome resistance.

L17 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2005:902693 HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER: 143:206406
TITLE: Anticancer therapies including glufosfamide
INVENTOR(S): Tidmarsh, George
PATENT ASSIGNEE(S): Threshold Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005076888	A2	20050825	WO 2005-US3370	20050204 <--
WO 2005076888	A3	20051027		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005213372	A1	20050825	AU 2005-213372	20050204 <--
AU 2005213372	B2	20110324		
CA 2554463	A1	20050825	CA 2005-2554463	20050204 <--
EP 1711188	A2	20061018	EP 2005-712714	20050204 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU				
CN 1917885	A	20070221	CN 2005-80004102	20050204 <--
BR 2005007463	A	20070710	BR 2005-7463	20050204 <--
JP 2007520562	T	20070726	JP 2006-552230	20050204 <--
ZA 2006006456	A	20080130	ZA 2006-6456	20050204 <--
NZ 549605	A	20100129	NZ 2005-549605	20050204 <--
IL 177136	A	20101130	IL 2005-177136	20050204 <--
MX 2006008954	A	20061002	MX 2006-8954	20060807 <--

	KR 2006131869	A	20061220	KR 2006-7017702	20060831	<--
	IN 2006KN02528	A	20070601	IN 2006-KN2528	20060904	<--
	NO 2006003987	A	20060906	NO 2006-3987	20060906	<--
	IN 2006KN02582	A	20070601	IN 2006-KN2582	20060908	<--
	US 20090247480	A1	20091001	US 2009-588409	20090506	<--
PRIORITY APPLN. INFO.:				US 2004-542494P P	20040206	<--
				WO 2005-US3370 W	20050204	

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Methods for the treatment of cancer are described. In particular, methods for treatment of cancer comprising administration of glufosfamide alone or in combination with another anticancer agent are disclosed. A cancer treatment method using a combination of glufosfamide and gemcitabine is claimed.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2005076888	A2	20050825	WO 2005-US3370	20050204	<--
	WO 2005076888	A3	20051027			
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
	AU 2005213372	A1	20050825	AU 2005-213372	20050204	<--
	AU 2005213372	B2	20110324			
	CA 2554463	A1	20050825	CA 2005-2554463	20050204	<--
	EP 1711188	A2	20061018	EP 2005-712714	20050204	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU					
	CN 1917885	A	20070221	CN 2005-80004102	20050204	<--
	BR 2005007463	A	20070710	BR 2005-7463	20050204	<--
	JP 2007520562	T	20070726	JP 2006-552230	20050204	<--
	ZA 2006006456	A	20080130	ZA 2006-6456	20050204	<--
	NZ 549605	A	20100129	NZ 2005-549605	20050204	<--
	IL 177136	A	20101130	IL 2005-177136	20050204	<--
	MX 2006008954	A	20061002	MX 2006-8954	20060807	<--
	KR 2006131869	A	20061220	KR 2006-7017702	20060831	<--
	IN 2006KN02528	A	20070601	IN 2006-KN2528	20060904	<--
	NO 2006003987	A	20060906	NO 2006-3987	20060906	<--
	IN 2006KN02582	A	20070601	IN 2006-KN2582	20060908	<--
	US 20090247480	A1	20091001	US 2009-588409	20090506	<--
PRAI	US 2004-542494P	P	20040206	<--		
	WO 2005-US3370	W	20050204			

IT Antitumor agents
Combination chemotherapy
Drug interactions
Human
Neoplasm
Pancreas, neoplasm
(anticancer therapies including glufosfamide)

IT Drug resistance
(antitumor, chemotherapy-refractory pancreatic cancer; anticancer therapies including glufosfamide)

IT Neoplasm
(metastasis; anticancer therapies including glufosfamide)
IT Antitumor agents
(resistance to, chemotherapy-refractory pancreatic cancer; anticancer therapies including glufosfamide)

L17 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2005:198694 HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER: 143:45
TITLE: Glufosfamide: beta-D-Glc-IPM, D 19575
AUTHOR(S): Anon.
CORPORATE SOURCE: Adis International Limited, Auckland, 65901, N. Z.
SOURCE: Drugs in R&D (2005), 6(1), 49-52
CODEN: DRDDFD; ISSN: 1174-5886
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Glufosfamide [D 19575, β-D-Glc-IPM] is a next-generation glucose conjugate of ifosfamide that is under development with Threshold Pharmaceuticals for the treatment of cancer. It is an alkylating agent in which isophosphoramide mustard, the alkylating metabolite of ifosfamide, is glycosidically linked to β-D-glucose. Cellular uptake of glufosfamide is mediated by a sodium-dependent transmembrane transporter protein of glucose and possibly also by other transporter proteins. Threshold is using its Metabolic Targeting technol. to exploit unique aspects of tumor metabolism, particularly the elevated glucose utilization of tumor cells to selectively target glufosfamide to the tumor site. Glufosfamide was originally developed from a research collaboration between Asta Medica (Degussa) and the Cancer Research Center (DKFZ) in Heidelberg, Germany. In Oct. 2001, Baxter International acquired the oncol. division of ASTA Medica, and renamed it Baxter Oncol. GmbH. According to its 2002 Annual Report, Baxter announced that it was terminating development of glufosfamide. Subsequently, Baxter and Threshold Pharmaceuticals entered into an exclusive licensing and development agreement in August 2003. Threshold has responsibility for the development and commercialization of glufosfamide, primarily for use as an antitumor agent. In addition, Baxter manufs. glufosfamide on Threshold's behalf. Threshold received fast-track status for glufosfamide from the US FDA in the treatment of metastatic pancreatic cancer refractory to gemcitabine in Nov. 2004. In Dec. 2004, Threshold initiated a phase I/II trial (TH-CR-301 Study) investigating glufosfamide in combination with gemcitabine as a first-line treatment of pancreatic cancer or advanced solid tumors. The phase I portion of the study may enroll up to 15 patients. The maximum tolerable dose combination determined will then be used in the phase 2 portion of the study. Up to 42 patients with advanced pancreatic cancer will be enrolled at various sites in the US, Latin America and Brazil. Previously, glufosfamide had been in phase II trials among patients with pancreatic carcinoma in Germany with Baxter Oncol. and with the EORTC in the UK as well as Greece. However, development has been discontinued.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
SO Drugs in R&D (2005), 6(1), 49-52
CODEN: DRDDFD; ISSN: 1174-5886
AB A review. Glufosfamide [D 19575, β-D-Glc-IPM] is a next-generation glucose conjugate of ifosfamide that is under development with Threshold Pharmaceuticals for the treatment of cancer. It is an alkylating agent in which isophosphoramide mustard, the alkylating metabolite of ifosfamide, is glycosidically linked to β-D-glucose.

Cellular uptake of glufosfamide is mediated by a sodium-dependent transmembrane transporter protein of glucose and possibly also by other transporter proteins. Threshold is using its Metabolic Targeting technol. to exploit unique aspects of tumor metabolism, particularly the elevated glucose utilization of tumor cells to selectively target glufosfamide to the tumor site. Glufosfamide was originally developed from a research collaboration between Asta Medica (Degussa) and the Cancer Research Center (DKFZ) in Heidelberg, Germany. In Oct. 2001, Baxter International acquired the oncol. division of ASTA Medica, and renamed it Baxter Oncol. GmbH. According to its 2002 Annual Report, Baxter announced that it was terminating development of glufosfamide. Subsequently, Baxter and Threshold Pharmaceuticals entered into an exclusive licensing and development agreement in August 2003. Threshold has responsibility for the development and commercialization of glufosfamide, primarily for use as an antitumor agent. In addition, Baxter manufs. glufosfamide on Threshold's behalf. Threshold received fast-track status for glufosfamide from the US FDA in the treatment of metastatic pancreatic cancer refractory to gemcitabine in Nov. 2004. In Dec. 2004, Threshold initiated a phase I/II trial (TH-CR-301 Study) investigating glufosfamide in combination with gemcitabine as a first-line treatment of pancreatic cancer or advanced solid tumors. The phase I portion of the study may enroll up to 15 patients. The maximum tolerable dose combination determined will then be used in the phase 2 portion of the study. Up to 42 patients with advanced pancreatic cancer will be enrolled at various sites in the US, Latin America and Brazil. Previously, glufosfamide had been in phase II trials among patients with pancreatic carcinoma in Germany with Baxter Oncol. and with the EORTC in the UK as well as Greece. However, development has been discontinued.

L17 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2004:1000261 HCAPLUS <<LOGINID::20110706>>

DOCUMENT NUMBER: 142:211703

TITLE: Ex vivo responsiveness of head and neck squamous cell carcinoma to glufosfamide, a novel alkylating agent

AUTHOR(S): Dollner, Ralph; Dietz, Andreas; Kopun, Marijana; Helbig, Matthias; Wallner, Frank; Granzow, Christof

CORPORATE SOURCE: Department of Otorhinolaryngology, Head and Neck Surgery, University of Leipzig, Leipzig, Germany

SOURCE: Anticancer Research (2004), 24(5A), 2947-2951
CODEN: ANTRD4; ISSN: 0250-7005

PUBLISHER: International Institute of Anticancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Glufosfamide is a novel alkylating agent in which the active metabolite of isophosphoramide mustard is glycosidically linked to β-D-glucose. Targeting the elevated glucose uptake of tumor cells expressing the SAAT1 glucose transporter, glufosfamide represents an attractive new drug for cancer chemotherapy. The present study investigates the ex vivo responsiveness of Head and Neck Squamous Cell Carcinoma (HNSCC) specimens to glufosfamide. Patients and Methods: Twenty-one unselected HNSCC specimens were investigated using a novel ex vivo colony formation assay to determine the epithelial drug response. The individual responsiveness to glufosfamide and to cis-platinum was determined Results: Five out of 21 evaluable HNSCC specimens were sensitive to glufosfamide. There was a tendency for glufosfamide sensitivity in platinum-resistant specimens and vice versa. Conclusion: The effectiveness of glufosfamide observed in the present ex vivo study suggests at least an equipotentiality of glufosfamide in comparison to cis-platinum. The potential clin. usefulness of glufosfamide in HNSCC warrants further evaluation.

OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS

RECORD (10 CITINGS)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Anticancer Research (2004), 24(5A), 2947-2951
CODEN: ANTRD4; ISSN: 0250-7005

AB Background: Glufosfamide is a novel alkylating agent in which the active metabolite of isophosphoramide mustard is glycosidically linked to β-D-glucose. Targeting the elevated glucose uptake of tumor cells expressing the SAAT1 glucose transporter, glufosfamide represents an attractive new drug for cancer chemotherapy. The present study investigates the ex vivo responsiveness of Head and Neck Squamous Cell Carcinoma (HNSCC) specimens to glufosfamide. Patients and Methods: Twenty-one unselected HNSCC specimens were investigated using a novel ex vivo colony formation assay to determine the epithelial drug response. The individual responsiveness to glufosfamide and to cis-platinum was determined Results: Five out of 21 evaluable HNSCC specimens were sensitive to glufosfamide. There was a tendency for glufosfamide sensitivity in platinum-resistant specimens and vice versa. Conclusion: The effectiveness of glufosfamide observed in the present ex vivo study suggests at least an equipotentiality of glufosfamide in comparison to cis-platinum. The potential clin. usefulness of glufosfamide in HNSCC warrants further evaluation.

IT Pharynx
(oropharynx; tendency for novel alkylating agent glufosfamide sensitivity in some platinum-resistant HNSCC patient specimen who had primary tumor location at oropharynx suggest at least equipotential effect of glufosfamide in comparison to cis-platinum)

IT Carcinoma
(pharyngeal squamous cell; tendency for novel alkylating agent glufosfamide sensitivity in some platinum-resistant HNSCC patient specimen who had primary tumor location at hypopharynx suggest at least equipotential effect of glufosfamide in comparison to cis-platinum)

IT Pharynx, neoplasm
(squamous cell carcinoma; tendency for novel alkylating agent glufosfamide sensitivity in some platinum-resistant HNSCC patient specimen who had primary tumor location at hypopharynx suggest at least equipotential effect of glufosfamide in comparison to cis-platinum)

IT Larynx
(tendency for novel alkylating agent glufosfamide sensitivity in some platinum-resistant HNSCC patient specimens who had primary tumor location at larynx suggest at least equipotential effect of glufosfamide in comparison to cis-platinum)

L17 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2004:187859 HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER: 141:271079
TITLE: Glufosfamide administered by 1-hour infusion as a second-line treatment for advanced non-small cell lung cancer a phase II trial of the EORTC-New Drug Development Group
AUTHOR(S): Giaccone, G.; Smit, E. F.; de Jonge, M.; Dansin, E.; Briasoulis, E.; Ardizzoni, A.; Douillard, J.-Y.; Spaeth, D.; Lacombe, D.; Baron, B.; Bachmann, P.; Fumoleau, P.
CORPORATE SOURCE: Departments of Medical Oncology and Lung Diseases, Vrije Universiteit Medical Center, Amsterdam, HV 1081, Neth.
SOURCE: European Journal of Cancer (2004), 40(5), 667-672

CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The activity of glufosfamide (β-D-glucosylisophosphoramide mustard) was tested in a multicenter phase II clin. trial in patients with advanced non-small cell lung cancer (NSCLC) who had received one prior line of platinum-based chemotherapy. Patients were treated with 5000 mg/m2 glufosfamide by a 1-h i.v. infusion every 3 wk following registration at the European Organization for Research and Treatment of Cancer (EORTC) Data Center. Patients were randomized between hydration and no hydration to evaluate the nephroprotective effects of forced diuresis. Patients experiencing ≥35 μmol/l increase of serum creatinine compared with baseline values were taken off the treatment. The Response evaluation criteria in solid tumors (RECIST) criteria were applied for the response assessment. Blood sampling was performed for a pharmacokinetic anal. 39 patients from seven institutions were registered and a median of three cycles was given (range 0-6) cycles; 20 patients were randomized to the hydration arm. Haematol. toxicity was mild, but treatment-related metabolic and electrolytic abnormalities and increases of serum creatinine occurred in several patients. Hydration did not have any significant influence on the plasma pharmacokinetics of glufosfamide and did not show any nephroprotective effect. Only one confirmed partial remission was observed (response rate 3%; 95% Confidence Interval (CI) 0-14) and 18 cases with stable disease (49%) were recorded as assessed by an independent panel. Median survival of all patients treated was 5.8 mo (95% CI 4.2-7.9). In conclusion, glufosfamide administered by a 1-h infusion every 3 wk has modest activity in advanced NSCLC patients after one prior platinum-based chemotherapy.

SO European Journal of Cancer (2004), 40(5), 667-672
CODEN: EJCAEL; ISSN: 0959-8049
AB The activity of glufosfamide (β-D-glucosylisophosphoramide mustard) was tested in a multicenter phase II clin. trial in patients with advanced non-small cell lung cancer (NSCLC) who had received one prior line of platinum-based chemotherapy. Patients were treated with 5000 mg/m2 glufosfamide by a 1-h i.v. infusion every 3 wk following registration at the European Organization for Research and Treatment of Cancer (EORTC) Data Center. Patients were randomized between hydration and no hydration to evaluate the nephroprotective effects of forced diuresis. Patients experiencing ≥35 μmol/l increase of serum creatinine compared with baseline values were taken off the treatment. The Response evaluation criteria in solid tumors (RECIST) criteria were applied for the response assessment. Blood sampling was performed for a pharmacokinetic anal. 39 patients from seven institutions were registered and a median of three cycles was given (range 0-6) cycles; 20 patients were randomized to the hydration arm. Haematol. toxicity was mild, but treatment-related metabolic and electrolytic abnormalities and increases of serum creatinine occurred in several patients. Hydration did not have any significant influence on the plasma pharmacokinetics of glufosfamide and did not show any nephroprotective effect. Only one confirmed partial remission was observed (response rate 3%; 95% Confidence Interval (CI) 0-14) and 18 cases with stable disease (49%) were recorded as assessed by an independent panel. Median survival of all patients treated was 5.8 mo (95% CI 4.2-7.9). In conclusion, glufosfamide administered by a 1-h infusion every 3 wk has modest activity in advanced NSCLC patients after one prior platinum-based chemotherapy.

L17 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2003:788578 HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER: 140:280885
TITLE: Glufosfamide administered using a 1-hour infusion given as first-line treatment for advanced pancreatic cancer. A phase II trial of the EORTC-new drug development group
AUTHOR(S): Briasoulis, E.; Pavlidis, N.; Terret, C.; Bauer, J.; Fiedler, W.; Schoffski, P.; Raoul, J.-L.; Hess, D.; Selvais, R.; Lacombe, D.; Bachmann, P.; Fumoleau, P.
CORPORATE SOURCE: School of Medicine, Medical Oncology Department, University of Ioannina, Ioannina, 451 10, Greece
SOURCE: European Journal of Cancer (2003), 39(16), 2334-2340
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The activity of glufosfamide (β-d-glucopyranosyl-N,N'-di-(2-chloroethyl)-phosphoric acid diamide) against pancreatic cancer was investigated in a multicenter, phase II clin. study. Chemotherapy-naive patients with advanced or metastatic disease were treated with glufosfamide (5 g/M2) using a 1-h i.v. infusion every 3 wk. Patients were randomized between active-hydration and normal fluids to evaluate the nephroprotective effect of forced diuresis. Patients experiencing >0.4 mg/dL (>35 μmol/l) increase in serum creatinine compared with their baseline value were taken off treatment for safety reasons. The evaluation of response was according to the Response evaluation criteria in solid tumors (RECIST). Blood sampling was performed for pharmacokinetic analyses. 35 Patients from 13 institutions were registered over a 13-mo period. A total of 114 treatment cycles (median 3, range 1-8) were administered to 34 patients; 18 patients were allocated to the hydration arm. Overall hematol. toxicity was mild. Metabolic acidosis occurred in 2 patients treated in the active-hydration arm, grade 3 hypokalemia was recorded in 5 patients and grade 3 hypophosphatemia in 4 patients. One patient had a grade 4 increase in serum creatinine level, concomitantly to disease progression. Active-hydration did not show a nephroprotective effect and the plasma pharmacokinetics (Pk) of glufosfamide was not significantly influenced by hydration. Two confirmed partial remissions (PR) were reported (response rate 5.9%, 95% Confidence Interval (CI) 0.7-19.7%) and 11 cases obtained disease stabilization (32.4%). An extra mural review panel confirmed all of the responses. Median overall survival was 5.3 mo (95% CI 3.9-7.1) and time to progression (TTP) was 1.4 mo (95% CI 1.3-2.7). In conclusion, glufosfamide administered using a 1-h infusion every 3 wk has a modest activity in advanced pancreatic adenocarcinoma. Hematol. toxicity is particularly mild, but regular monitoring of renal function is recommended.
OS.CITING REF COUNT: 29 THERE ARE 29 CAPLUS RECORDS THAT CITE THIS RECORD (29 CITINGS)
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI Glufosfamide administered using a 1-hour infusion given as first-line treatment for advanced pancreatic cancer. A phase II trial of the EORTC-new drug development group
SO European Journal of Cancer (2003), 39(16), 2334-2340
CODEN: EJCAEL; ISSN: 0959-8049
AB The activity of glufosfamide (β-d-glucopyranosyl-N,N'-di-(2-chloroethyl)-phosphoric acid diamide) against pancreatic cancer was investigated in a multicenter, phase II clin. study. Chemotherapy-naive patients with advanced or metastatic disease were treated with glufosfamide (5 g/M2) using a 1-h i.v. infusion every 3 wk. Patients

were randomized between active-hydration and normal fluids to evaluate the nephroprotective effect of forced diuresis. Patients experiencing >0.4 mg/dL (>35 μmol/l) increase in serum creatinine compared with their baseline value were taken off treatment for safety reasons. The evaluation of response was according to the Response evaluation criteria in solid tumors (RECIST). Blood sampling was performed for pharmacokinetic analyses. 35 Patients from 13 institutions were registered over a 13-mo period. A total of 114 treatment cycles (median 3, range 1-8) were administered to 34 patients; 18 patients were allocated to the hydration arm. Overall hematol. toxicity was mild. Metabolic acidosis occurred in 2 patients treated in the active-hydration arm, grade 3 hypokalemia was recorded in 5 patients and grade 3 hypophosphatemia in 4 patients. One patient had a grade 4 increase in serum creatinine level, concomitantly to disease progression. Active-hydration did not show a nephroprotective effect and the plasma pharmacokinetics (Pk) of glufosfamide was not significantly influenced by hydration. Two confirmed partial remissions (PR) were reported (response rate 5.9%, 95% Confidence Interval (CI) 0.7-19.7%) and 11 cases obtained disease stabilization (32.4%). An extra mural review panel confirmed all of the responses. Median overall survival was 5.3 mo (95% CI 3.9-7.1) and time to progression (TTP) was 1.4 mo (95% CI 1.3-2.7). In conclusion, glufosfamide administered using a 1-h infusion every 3 wk has a modest activity in advanced pancreatic adenocarcinoma. Hematol. toxicity is particularly mild, but regular monitoring of renal function is recommended.

ST glufosfamide antitumor pancreas

IT Pancreas, neoplasm
(adenocarcinoma; safety and efficacy of glufosfamide administered using 1-h infusion given as first-line treatment for advanced pancreatic cancer in humans)

IT Kidney
(function; safety and efficacy of glufosfamide administered using 1-h infusion given as first-line treatment for advanced pancreatic cancer in humans)

IT Acidosis
(metabolic; safety and efficacy of glufosfamide administered using 1-h infusion given as first-line treatment for advanced pancreatic cancer in humans)

IT Carcinoma
(pancreatic adenocarcinoma; safety and efficacy of glufosfamide administered using 1-h infusion given as first-line treatment for advanced pancreatic cancer in humans)

IT Antitumor agents
Chemotherapy
Human
(safety and efficacy of glufosfamide administered using 1-h infusion given as first-line treatment for advanced pancreatic cancer in humans)

IT 7440-09-7, Potassium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hypokalemia; safety and efficacy of glufosfamide administered using 1-h infusion given as first-line treatment for advanced pancreatic cancer in humans)

IT 14265-44-2, Phosphate, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hypophosphatemia; safety and efficacy of glufosfamide administered using 1-h infusion given as first-line treatment for advanced pancreatic cancer in humans)

IT 132682-98-5, Glufosfamide
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(safety and efficacy of glufosfamide administered using 1-h infusion given as first-line treatment for advanced pancreatic cancer in humans)
IT 60-27-5, Creatinine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(safety and efficacy of glufosfamide administered using 1-h infusion given as first-line treatment for advanced pancreatic cancer in humans)

L17 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2000:789787 HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER: 135:219
TITLE: Phase I trial of 6-hour infusion of glufosfamide, a new alkylating agent with potentially enhanced selectivity for tumors that overexpress transmembrane glucose transporters: A study of the European Organization for Research and Treatment of Cancer Early Clinical Studies Group
AUTHOR(S): Briasoulis, Evangelos; Judson, Ian; Pavlidis, Nicholas; Beale, Philip; Wanders, Jantien; Groot, Yvonne; Veerman, Gijbert; Schuessler, Martina; Niebch, Georg; Siamopoulos, Konstantinos; Tzamakou, Eleftheria; Rammou, Dimitra; Wolf, Lisa; Walker, Ruth; Hanauske, Axel
CORPORATE SOURCE: Department of Medical Oncology, School of Medicine, University of Iounnina, Ioannina, 451101, Greece
SOURCE: Journal of Clinical Oncology (2000), 18(20), 3535-3544
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aim of this study was to determine the maximum-tolerated dose (MTD), the principal toxicities, and the pharmacokinetics of 6-h infusion of glufosfamide (beta-D-glucosylisophosphoramide mustard; D-19575), a novel alkylating agent with the potential to target the glucose transporter system. Twenty-one patients (10 women and 11 men; median age, 56 yr) with refractory solid tumors were treated with doses ranging from 800 to 6,000 mg/m2. Glufosfamide was administered every 3 wk as a two-step (fast/slow) i.v. infusion over a 6-h period. All patients underwent pharmacokinetic sampling at the first course. The MTD was 6,000 mg/m2. At this dose, two of six patients developed a reversible, dose-limiting renal tubular acidosis and a slight increase in serum creatinine the week after the second and third courses of treatment, resp., whereas three of six patients experienced short-lived grade 4 neutropenia/leukopenia. Other side effects were generally mild. Pharmacokinetics indicated linearity of area under the time-vs.-concentration curve against dose over the dose range studied and a short elimination half-life. There was clear evidence of antitumor activity, with a long-lasting complete response of an advanced pancreatic adenocarcinoma and minor tumor shrinkage of two refractory colon carcinomas and one heavily pretreated breast cancer. The principal toxicity of 6-h infusion of glufosfamide is reversible renal tubular acidosis, the MTD is 6,000 mg/m2, and the recommended phase II dose is 4,500 mg/m2. Close monitoring of serum potassium and creatinine levels is suggested for patients receiving glufosfamide for early detection of possible renal toxicity. Evidence of antitumor activity in resistant carcinomas warrants further clin. exploration of glufosfamide in phase II studies.

OS.CITING REF COUNT: 29 THERE ARE 29 CAPLUS RECORDS THAT CITE THIS RECORD (29 CITINGS)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Phase I trial of 6-hour infusion of glufosfamide, a new alkylating agent with potentially enhanced selectivity for tumors that overexpress transmembrane glucose transporters: A study of the European Organization for Research and Treatment of Cancer Early Clinical Studies Group

SO Journal of Clinical Oncology (2000), 18(20), 3535-3544
CODEN: JCONDN; ISSN: 0732-183X

AB Aim of this study was to determine the maximum-tolerated dose (MTD), the principal toxicities, and the pharmacokinetics of 6-h infusion of glufosfamide (beta-D-glucosylisophosphoramide mustard; D-19575), a novel alkylating agent with the potential to target the glucose transporter system. Twenty-one patients (10 women and 11 men; median age, 56 yr) with refractory solid tumors were treated with doses ranging from 800 to 6,000 mg/m2. Glufosfamide was administered every 3 wk as a two-step (fast/slow) i.v. infusion over a 6-h period. All patients underwent pharmacokinetic sampling at the first course. The MTD was 6,000 mg/m2. At this dose, two of six patients developed a reversible, dose-limiting renal tubular acidosis and a slight increase in serum creatinine the week after the second and third courses of treatment, resp., whereas three of six patients experienced short-lived grade 4 neutropenia/leukopenia. Other side effects were generally mild. Pharmacokinetics indicated linearity of area under the time-vs.-concentration curve against dose over the dose range studied and a short elimination half-life. There was clear evidence of antitumor activity, with a long-lasting complete response of an advanced pancreatic adenocarcinoma and minor tumor shrinkage of two refractory colon carcinomas and one heavily pretreated breast cancer. The principal toxicity of 6-h infusion of glufosfamide is reversible renal tubular acidosis, the MTD is 6,000 mg/m2, and the recommended phase II dose is 4,500 mg/m2. Close monitoring of serum potassium and creatinine levels is suggested for patients receiving glufosfamide for early detection of possible renal toxicity. Evidence of antitumor activity in resistant carcinomas warrants further clin. exploration of glufosfamide in phase II studies.

ST glufosfamide D19575 pharmacokinetics antitumor solid tumor; alkylating agent antitumor solid tumor

IT Alkylating agents, biological
(glufosfamide (D-19575), a new alkylating agent, in treatment of solid tumor in humans)

IT Drug delivery systems
(infusions, i.v.; glufosfamide (D-19575), a new alkylating agent, in treatment of solid tumor in humans)

IT Antitumor agents
(solid tumor; glufosfamide (D-19575), a new alkylating agent, in treatment of solid tumor in humans)

IT 132682-98-5, Glufosfamide
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(glufosfamide (D-19575), a new alkylating agent, in treatment of solid tumor in humans)

L17 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2000:124696 HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER: 132:155964

TITLE: Biodegradability of antineoplastic compounds in screening tests: influence of glucosidation and of stereochemistry
AUTHOR(S): Kummerer, K.; Al-Ahmad, A.; Bertram, B.; Wiessler, M.
CORPORATE SOURCE: Institute of Environmental Medicine and Hospital Epidemiology, University Hospital University of Freiburg, Freiburg, D-79106, Germany
SOURCE: Chemosphere (2000), 40(7), 767-773
CODEN: CMSHAF; ISSN: 0045-6535
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Some pharmaceuticals such as antineoplastics are carcinogenic, mutagenic, teratogenic, and fetotoxic. Antineoplastics and their metabolites are excreted by patients into wastewater. In laboratory testing, the frequently used isomeric anti-tumor agents cyclophosphamide (CP) and ifosfamide (IF) were shown to be non-biodegradable. They are not eliminated in municipal wastewater treatment plants and therefore are detected in the effluent. Structural related compds. are β-D-glucosylisophosphoramidmustard (β-D-Glc-IPM; INN = glufosfamide) and β-L-glucosylisophosphoramidmustard (β-L-Glc-IPM). β-L-Glc-IPM has no antineoplastic effects whereas β-D-Glc-IPM is active against tumors. In contrast to IF and CP and almost all other investigated antineoplastics, β-D-Glc-IPM is inherently biodegradable. Improved biodegradability of β-D-Glc-IPM compared to IF showed that reducing the impact of pharmaceuticals on the aquatic environment is feasible by changing the chemical structure of a given compound exerting a similar mode of action and therapeutic activity. Stereochem. may be crucial for pharmaceutical activity of compds. and for their biodegradability in the environment.

OS.CITING REF COUNT: 41 THERE ARE 41 CAPLUS RECORDS THAT CITE THIS RECORD (41 CITINGS)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Chemosphere (2000), 40(7), 767-773
CODEN: CMSHAF; ISSN: 0045-6535
AB Some pharmaceuticals such as antineoplastics are carcinogenic, mutagenic, teratogenic, and fetotoxic. Antineoplastics and their metabolites are excreted by patients into wastewater. In laboratory testing, the frequently used isomeric anti-tumor agents cyclophosphamide (CP) and ifosfamide (IF) were shown to be non-biodegradable. They are not eliminated in municipal wastewater treatment plants and therefore are detected in the effluent. Structural related compds. are β-D-glucosylisophosphoramidmustard (β-D-Glc-IPM; INN = glufosfamide) and β-L-glucosylisophosphoramidmustard (β-L-Glc-IPM). β-L-Glc-IPM has no antineoplastic effects whereas β-D-Glc-IPM is active against tumors. In contrast to IF and CP and almost all other investigated antineoplastics, β-D-Glc-IPM is inherently biodegradable. Improved biodegradability of β-D-Glc-IPM compared to IF showed that reducing the impact of pharmaceuticals on the aquatic environment is feasible by changing the chemical structure of a given compound exerting a similar mode of action and therapeutic activity. Stereochem. may be crucial for pharmaceutical activity of compds. and for their biodegradability in the environment.

L17 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2000:123131 HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER: 133:53248
TITLE: Mechanistic aspects of the cytotoxic activity of glufosfamide, a new tumour therapeutic agent
AUTHOR(S): Seker, H.; Bertram, B.; Burkle, A.; Kaina, B.; Pohl,

J.; Koepsell, H.; Wiessler, M.
CORPORATE SOURCE: Division of Molecular Toxicology, German Cancer Research Center, Heidelberg, Germany
SOURCE: British Journal of Cancer (2000), 82(3), 629-634
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB β-D-Glucosyl-ifosfamide mustard (D 19575, glc-IPM, INN = glufosfamide) is a new agent for cancer chemotherapy. Its mode of action, which is only partly understood, was investigated at the DNA level. In the breast carcinoma cell line MCF7 glufosfamide inhibited both the synthesis of DNA and protein in a dose-dependent manner, as shown by the decreased incorporation of [3H-methyl]-thymidine into DNA and [14C]-methionine into protein of these cells. Treatment of MCF7 cells with 50 μM glufosfamide was sufficient to trigger poly(ADP-ribose) polymerase (PARP) activation, as revealed by immunofluorescence anal. Both CHO-9 cells, which are O6-methylguanine-DNA methyltransferase (MGMT)-deficient, and an isogenic derivative, which has a high level of MGMT, showed the same cytotoxic response to β-D-glc-IPM, indicating that the O6 position of guanine is not the critical target for cytotoxicity. By contrast, a sharp decrease in survival of cross-link repair deficient CL-V5 B cells was observed already at concns. of 0.1 mM β-D-glc-IPM, whereas the wild-type V79 cells showed a 90% reduction in survival only after treatment with 0.5 mM of this compound The therapeutically inactive β-L-enantiomer of glufosfamide also showed genotoxic effects in the same assays but at much higher doses. This was probably due to small amts. of ifosfamide mustard formed under the conditions of incubation. The results indicate that the DNA crosslinks are the most critical cytotoxic lesions induced by β-D-glc-IPM.
OS.CITING REF COUNT: 29 THERE ARE 29 CAPLUS RECORDS THAT CITE THIS RECORD (29 CITINGS)
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Mechanistic aspects of the cytotoxic activity of glufosfamide, a new tumour therapeutic agent
SO British Journal of Cancer (2000), 82(3), 629-634
CODEN: BJCAAI; ISSN: 0007-0920
ST glufosfamide cytotoxicity tumor DNA crosslink
IT DNA
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(crosslinked; mechanistic aspects of cytotoxic activity of new tumor therapeutic agent glufosfamide)
IT Antitumor agents
DNA formation
DNA repair
Translation, genetic
(mechanistic aspects of cytotoxic activity of new tumor therapeutic agent glufosfamide)
IT 132682-98-5, Glufosfamide 213888-58-5
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(mechanistic aspects of cytotoxic activity of new tumor therapeutic agent glufosfamide)
IT 9055-67-8, Poly(ADP-ribose) polymerase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mechanistic aspects of cytotoxic activity of new tumor

therapeutic agent glufosfamide)

L17 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 1999:549286 HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER: 131:155041
TITLE: A sugar transporter capable of transporting saccharide-coupled medicaments and the gene encoding it
INVENTOR(S): Koepsell, Hermann; Wiessler, Manfred
PATENT ASSIGNEE(S): Deutsches Krebsforschungszentrum Stiftung Des Offentlichen Rechts, Germany
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9942477	A2	19990826	WO 1999-DE535	19990218 <--
WO 9942477	A3	20000330		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19806803	A1	19991125	DE 1998-19806803	19980218 <--
EP 1056857	A2	20001206	EP 1999-915493	19990218 <--
R: AT, BE, CH, DE, ES, FR, GB, LI, LU, NL, SE				
JP 2002504318	T	20020212	JP 2000-532429	19990218 <--
PRIORITY APPLN. INFO.:			DE 1998-19806803 A	19980218 <--
			WO 1999-DE535 W	19990218 <--

AB The gene for a sodium-dependent sugar transporter protein SAAT1 of the SGLT family that is capable of transporting glycosides of drugs into cells is described. The transporter can be used to deliver drugs to tissues it is found in and assays for the protein are described. Tumors or tissues carrying the transporter can be effectively targeted by delivering drugs as glycosides specific for it. The protein can transport the cytostatic glufosfamide and β-D-glucosyl gentisic acid Me ester whereas other members of the family cannot. T-84 cells, which carry the SAAT1 transporter were shown to take up glufosfamide through it. The gene can be used to manufacture the protein in a prokaryotic or eukaryotic host or in gene therapy, e.g. to make tumor cells more sensitive to chemotherapeutics by delivering as the less toxic glycosides. Antibodies to the protein are prepared

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

PI WO 9942477 A2 19990826

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9942477	A2	19990826	WO 1999-DE535	19990218 <--
WO 9942477	A3	20000330		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19806803	A1	19991125	DE 1998-19806803	19980218 <--
EP 1056857	A2	20001206	EP 1999-915493	19990218 <--
R: AT, BE, CH, DE, ES, FR, GB, LI, LU, NL, SE				
JP 2002504318	T	20020212	JP 2000-532429	19990218 <--
PRAI DE 1998-19806803	A	19980218 <--		
WO 1999-DE535	W	19990218 <--		

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SGLT family that is capable of transporting glycosides of drugs into cells is described. The transporter can be used to deliver drugs to tissues it is found in and assays for the protein are described. Tumors or tissues carrying the transporter can be effectively targeted by delivering drugs as glycosides specific for it. The protein can transport the cytostatic glufosfamide and β-D-glucosyl gentisic acid Me ester whereas other members of the family cannot. T-84 cells, which carry the SAAT1 transporter were shown to take up glufosfamide through it. The gene can be used to manufacture the protein in a prokaryotic or eukaryotic host or in gene therapy, e.g. to make tumor cells more sensitive to chemotherapeutics by delivering as the less toxic glycosides. Antibodies to the protein are prepared

L17 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 1998:581194 HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER: 129:269950
ORIGINAL REFERENCE NO.: 129:54857a,54860a
TITLE: Possible role of the cytosolic β-glucosidase in the metabolism of saccharide-coupled platinum and ifosfamide mustard in tumor cells
AUTHOR(S): Seker, H.; Bertram, B.; Menzler, S.; Wiessler, M.
CORPORATE SOURCE: Div. Mol. Toxicol., German Cancer Res. Center, Heidelberg, Germany
SOURCE: Mediterranean Congress of Chemotherapy, 10th, Antalya, Turk., Oct. 20-25, 1996 (1996), 381-385. Editor(s): Berkarda, Buelent. Monduzzi Editore: Bologna, Italy. CODEN: 66MTAV
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The in vitro enzyme tests with different types of enzymes (phosphatases, esterases, lipases, etc.) showed that saccharide conjugates of platinum (Pt) and ifosfamide mustard (IPM), i.e. β-D-Glc-IPM, β-D-Gal-IPM, β-D-Glc-EPM (β-D-Glc-IPM with Et spacer), and β-D-Gal-Pt, are only substrates for β-glucosidases. They also showed that β-D-Glc-IPM is also a substrate for a sec. mammalian β-glucosidase, the lysosomal β-glucosidase (glucocerebrosidase). However, because of its location in the lysosomes, its acidic pH range and the fact that the hydrophilic cytostatic compound would have to pass the lysosomal membrane, there is doubt that the lysosomal enzyme is involved in the activation of the compds. β-L-Glc-IPM, α-D-Gal-IPM, and 6-Iso-β-D-Glc-IPM could not be split by none of the two glucosidases. Finding of this study confirm the assumption that the cytosolic enzyme might be involved in the activation of these compds.
OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
SO Mediterranean Congress of Chemotherapy, 10th, Antalya, Turk., Oct. 20-25, 1996 (1996), 381-385. Editor(s): Berkarda, Buelent. Publisher: Monduzzi Editore, Bologna, Italy. CODEN: 66MTAV
IT 132682-97-4 132682-98-5 213888-57-4 213888-58-5
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cytosolic β-glucosidase activation of saccharide-coupled platinum and ifosfamide mustard in tumor cells)

L17 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 1998:292174 HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER: 129:89860
ORIGINAL REFERENCE NO.: 129:18335a,18338a

TITLE: Assessment of glucosylifosfamide mustard biodistribution in rats with prostate adenocarcinomas by means of in vivo 31P NMR and in vitro uptake experiments

AUTHOR(S): Haberkorn, Uwe; Krems, Boris; Gerlach, Ludwig; Bachert, Peter; Morr, Iris; Wiessler, Manfred; Van Kaick, Gerhard

CORPORATE SOURCE: Departments of Oncological Diagnostics and Therapy, German Cancer Research Center (DKFZ), Heidelberg, FRG-69120, Germany

SOURCE: Magnetic Resonance in Medicine (1998), 39(5), 754-761
CODEN: MRMEEN; ISSN: 0740-3194

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A combined in vitro/in vivo study was performed to evaluate the possible application of phosphorus (31P) NMR spectroscopy for therapy monitoring and to investigate glucosylifosfamide mustard (Glc-IPM) transport and biodistribution by radiotracer techniques. Dynamic in vivo 31P NMR measurements were performed in rats with prostate adenocarcinoma after i.v. injection of 1 mmol/kg body weight (bw) of ifosfamide (IFO) (n = 4) and 1 mmol/kg bw (n = 4) or 2.15 mmol/kg bw (n = 9) of Glc-IPM. In a biodistribution study with 14C-labeled Glc-IPM and a final dose of 0.8 mmol Glc-IPM/kg bw, the animals were killed 5, 30, 60, and 120 min after drug administration, an ethanol extraction was performed from several tissues, and the dose per g tissue was calculated The same tumor cell line was used in saturation and competition expts. to further elucidate the transport mechanism. The 31P NMR signals of IFO and Glc-IPM showed no overlap with the endogenous phosphorus peaks. A rapid washout with a half-life between 25.9±5.6 min for the lower dose and 34.3±4.2 min for the higher dose of Glc-IPM was observed in the tumor. No statistically significant change of the pH value was observed during the examination period. The β-nucleoside 5'-triphosphate (NTP)/inorg. phosphate (Pi) signal intensity ratio showed a tendency to decrease but without statistical significance. A rapid elimination was demonstrated by both the noninvasive NMR technique and the biodistribution study. No saturation was found in vitro for the Glc-IPM uptake, even at the concentration of 5 mM. Furthermore, the Glc-IPM uptake was not inhibited by the presence of 2-deoxyglucose and vice versa. The data show that the pharmacokinetics of Glc-IPM in the tumor can be followed in vivo by 31P NMR. The results presented are evidence for diffusion as the transport mechanism for Glc-IPM in this tumor model. However, the better visualization of Glc-IPM as compared to ifosfamide may be due to metabolic trapping of a neg. charged metabolite after deglycosylation.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Magnetic Resonance in Medicine (1998), 39(5), 754-761
CODEN: MRMEEN; ISSN: 0740-3194

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L17 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER:	1998:209114 HCAPLUS <<LOGINID::20110706>>
DOCUMENT NUMBER:	128:316882
ORIGINAL REFERENCE NO.:	128:62621a,62624a
TITLE:	Transport of the new chemotherapeutic agent β-D-glucosylisophosphoramide mustard (D-19575) into tumor cells is mediated by the Na+-D-glucose cotransporter SAAT1
AUTHOR(S):	Veyhl, Maike; Wagner, Katharina; Volk, Christopher; Gorboulev, Valentin; Baumgarten, Katharina; Weber, Wolf-Michael; Schaper, Marianne; Bertram, Barbara; Wiessler, Manfred; Koepsell, Hermann
CORPORATE SOURCE:	Institute Anatomy, Bayerische Julius-Maximilians-Universitat, Wurzburg, 97070, Germany
SOURCE:	Proceedings of the National Academy of Sciences of the United States of America (1998), 95(6), 2914-2919 CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER:	National Academy of Sciences
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB For β-D-glucosylisophosphoramide mustard (β-D-Glc-IPM), a new alkylating drug in which isophosphoramide mustard is stabilized, a higher selectivity and lower myelotoxicity was observed than for the currently used cytostatic ifosfamide. Because β-D-Glc-IPM is hydrophilic and does not diffuse passively through the lipid bilayer, we investigated whether a transporter may be involved in the cellular uptake. A variety of cloned Na+-sugar cotransporters were expressed in Xenopus oocytes, and uptake measurements were performed. By tracer uptake and elec. measurements it was found that β-D-Glc-IPM was transported by the low-affinity Na+-D-glucose cotransporter SAAT1, which had been cloned from pig and is also expressed in humans. At membrane potentials between -50 and -150 mV, a 10-fold higher substrate affinity (Km ≈ 0.25 mM) and a 10-fold lower Vmax value were estimated for β-D-Glc-IPM transport than for the transport of D-glucose or methyl-α-D-glucopyranoside (AMG). Transport of β-D-Glc-IPM and glucose by SAAT1 is apparently performed by the same mechanism because similar sodium dependence, dependence on membrane potential, electrogenicity, and phlorizin inhibition were determined for β-D-Glc-IPM, D-glucose, and AMG. Transcription of human SAAT1 was demonstrated in various human carcinomas and tumor cell lines. In one of these, the human carcinoma cell line T84, phlorizin inhibitable uptake of β-D-Glc-IPM was demonstrated with substrate saturation and an apparent Km of 0.4 mM. The data suggest that the Na+-D-glucose cotransporter SAAT1 transports β-D-Glc-IPM into human tumor cells and may accumulate the

drug in the cells. They provide an example for drug targeting by employing a plasma membrane transporter.

OS.CITING REF COUNT: 65 THERE ARE 65 CAPLUS RECORDS THAT CITE THIS RECORD (65 CITINGS)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Transport of the new chemotherapeutic agent β-D-glucosylisophosphoramide mustard (D-19575) into tumor cells is mediated by the Na+-D-glucose cotransporter SAAT1

SO Proceedings of the National Academy of Sciences of the United States of America (1998), 95(6), 2914-2919
CODEN: PNASA6; ISSN: 0027-8424

ST antitumor D 19575 transport tumor

IT Biological transport
(drug; transport of antitumor D-19575 into tumor cells is mediated by the sodium-glucose cotransporter SAAT1)

IT Transport proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(glucose-sodium-cotransporting, SAAT1; transport of antitumor D -19575 into tumor cells is mediated by the sodium-glucose cotransporter SAAT1)

IT Antitumor agents
(transport of antitumor D-19575 into tumor cells is mediated by the sodium-glucose cotransporter SAAT1)

IT 132682-98-5, D-19575
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transport of antitumor D-19575 into tumor cells is mediated by the sodium-glucose cotransporter SAAT1)

L17 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 1995:475169 HCAPLUS <<LOGINID::20110706>>

DOCUMENT NUMBER: 122:281554

ORIGINAL REFERENCE NO.: 122:51051a,51054a

TITLE: D-19575 - a sugar-linked isophosphoramide mustard derivative exploiting transmembrane glucose transport

AUTHOR(S): Pohl, J.; Bertram, B.; Hilgard, P.; Nowrousian, M.R.; Stueben, J.; Wiessler, M.

CORPORATE SOURCE: Asta Medica AG, Frankfurt/Main, D-60314, Germany

SOURCE: Cancer Chemotherapy and Pharmacology (1995), 35(5), 364-70
CODEN: CCPHDZ; ISSN: 0344-5704

DOCUMENT TYPE: Journal

LANGUAGE: English

AB D-19575 is a glucose derivative of ifosfamide mustard with a broad spectrum of antitumor activity in animal models. In comparison with ifosfamide, D-19575 is less toxic and is better tolerated by tumor-bearing animals, achieving a better therapeutic efficacy. D-19575 is directly cytotoxic in vitro, in contrast to ifosfamide, and it is possible to modulate this cytotoxicity by inhibition of transmembrane glucose transporters. Correspondingly, renal resorption of filtered D-19575 could be blocked by pre- and cotreatment with phlorizin, resulting in a higher urinary excretion of the unchanged drug. The toxicity to white blood cells, colony-forming units (CFU-C), and spleen-cell colony-forming units (CFU-S) is considerably lower for D-19575 as compared with ifosfamide. In conclusion, D-19575 is a new alkylating cytotoxic agent with increased antitumor selectivity, probably caused by an active transmembrane transport mechanism.

OS.CITING REF COUNT: 42 THERE ARE 42 CAPLUS RECORDS THAT CITE THIS

RECORD (42 CITINGS)

SO Cancer Chemotherapy and Pharmacology (1995), 35(5), 364-70
CODEN: CCPHDZ; ISSN: 0344-5704

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